

**Supplementary Table 1.** Population characteristics according nitrosyl-heme intake in men within European Prospective Investigation into Cancer and Nutrition

| Men                                                   |                         | Nitrosyl-heme intake (µg/d) |          |          |          |
|-------------------------------------------------------|-------------------------|-----------------------------|----------|----------|----------|
|                                                       |                         | N (%)                       | p25      | Median   | p75      |
| <b>Total</b>                                          |                         | 109,120 (29.7)              | 379.73   | 1,006.80 | 2,047.18 |
| <b>Age (y)</b>                                        |                         |                             |          |          |          |
|                                                       | <33                     | 4,272 (3.9)                 | 21.40    | 269.01   | 1,443.62 |
|                                                       | ≥33-<44                 | 17,156 (15.7)               | 280.83   | 910.87   | 2,101.7  |
|                                                       | ≥44 - <54               | 38,751 (35.5)               | 430.44   | 1,071.93 | 2,100.53 |
|                                                       | ≥54- <64                | 40,003 (36.7)               | 492.22   | 1,161.93 | 2,157.32 |
|                                                       | ≥64                     | 8,938 (8.2)                 | 215.97   | 555.24   | 1,208.10 |
| <b>BMI (kg/m2)</b>                                    |                         |                             |          |          |          |
|                                                       | <25                     | 38,461 (35.2)               | 249.83   | 800.74   | 1,861.44 |
|                                                       | >25-30                  | 53,779 (49.3)               | 431.92   | 1,064.96 | 2,075.50 |
|                                                       | >30                     | 16,880 (15.5)               | 543.17   | 1,237.59 | 2,352.82 |
| <b>Country</b>                                        |                         |                             |          |          |          |
|                                                       | France                  | /                           | /        | /        | /        |
|                                                       | Italy                   | 14,032 (12.9)               | 279.71   | 537.94   | 952.01   |
|                                                       | Spain                   | 15,139 (13.9)               | 385.71   | 894.77   | 1,637.71 |
|                                                       | UK                      | 22,850 (20.9)               | 42.80    | 254.16   | 598.63   |
|                                                       | The Netherlands         | 9,627 (8.8)                 | 686.25   | 1,415.98 | 2,472.02 |
|                                                       | Germany                 | 21,178 (19.4)               | 1,395.43 | 2,368.99 | 3,832.29 |
|                                                       | Denmark                 | 26,294 (24.1)               | 882.44   | 1,467.05 | 2,284.12 |
| <b>Waist circumference (cm)<sup>a</sup></b>           |                         |                             |          |          |          |
|                                                       | Normal                  | 85,274 (78.1)               | 338.96   | 930.36   | 1,955.65 |
|                                                       | High                    | 23,846 (21.9)               | 563.98   | 1261.81  | 2,337.58 |
| <b>Cambridge Physical Activity Index (Met-h/week)</b> |                         |                             |          |          |          |
|                                                       | Inactive                | 18,357 (16.8)               | 300.00   | 771.43   | 1,814.27 |
|                                                       | Moderately Inactive     | 32,821 (30.1)               | 371.38   | 961.58   | 1,968.52 |
|                                                       | Moderately Active       | 25,955 (23.8)               | 392.92   | 1,042.76 | 2,064.67 |
|                                                       | Active                  | 28,984 (26.6)               | 450.30   | 1,164.42 | 2,215.86 |
|                                                       | Missing/Unknown         | 3,003 (2.8)                 | 435.21   | 1,116.60 | 2,068.44 |
| <b>Educational level</b>                              |                         |                             |          |          |          |
|                                                       | None                    | 4,183 (3.8)                 | 377.79   | 910.03   | 1,728.62 |
|                                                       | Primary School          | 29,610 (27.1)               | 531.15   | 1,195.79 | 2,250.46 |
|                                                       | Technical, professional | 27,851 (25.5)               | 475.02   | 1,172.77 | 2,260.60 |
|                                                       | Secondary School        | 12,736 (11.7)               | 302.10   | 735.77   | 1,512.72 |
|                                                       | Longer Education        | 31,008 (28.4)               | 280.47   | 952.73   | 2,042.84 |
|                                                       | Not specified           | 3,732 (3.4)                 | 61.19    | 314.64   | 690.07   |
| <b>Smoking status</b>                                 |                         |                             |          |          |          |
|                                                       | Never                   | 34,402 (31.5)               | 269.01   | 821.37   | 860.96   |
|                                                       | Former                  | 41,094 (37.7)               | 375.48   | 978.91   | 2,013.54 |
|                                                       | Current                 | 32,452 (27.7)               | 551.36   | 1,239.25 | 2,277.27 |
|                                                       | Missing/Unknown         | 1,172 (1.1)                 | 217.56   | 497.25   | 867.39   |
| <b>Alcohol lifetime (g/day)<sup>b</sup></b>           |                         |                             |          |          |          |
|                                                       | Non alcohol             | 1,301 (1.2)                 | 222.94   | 589.22   | 1,319.46 |
|                                                       | Never heavy             | 100,239 (91.9)              | 373.38   | 995.68   | 2,028.75 |
|                                                       | Heavy                   | 7,580 (6.9)                 | 537.00   | 1,235.03 | 2,380.76 |
| <b>Family history of colorectal cancer</b>            |                         |                             |          |          |          |
|                                                       | Yes                     | 23,974 (22.0)               | 274.29   | 639.23   | 1,247.57 |
|                                                       | No                      | 1,611 (1.5)                 | 271.74   | 610.20   | 1,138.11 |
|                                                       | Not specified           | 83,535 (76.6)               | 435.03   | 1,179.18 | 2,278.2  |
| <b>Calcium (mg/day)<sup>c</sup></b>                   |                         |                             |          |          |          |
|                                                       | Very Low                | 28,357 (26.0)               | 411.17   | 1,107.29 | 2,155.87 |
|                                                       | Low                     | 29,510 (27.0)               | 387.92   | 1,013.57 | 2,057.43 |
|                                                       | Normal                  | 51,253 (47.0)               | 360.71   | 950.24   | 1,975.18 |

**Fibre (g/day)**

|     |               |        |          |          |
|-----|---------------|--------|----------|----------|
| <30 | 82,449 (75.6) | 393.12 | 982.03   | 1,986.72 |
| ≥30 | 26,671 (24.4) | 321.03 | 1,095.46 | 2,213.78 |

<sup>a</sup>Waist circumference (cm) (normal: <102 cm; high: ≥102 cm)

<sup>b</sup>Alcohol lifetime (g/day) (0=no alcohol in the past, i.e. at all ages in the past the alcohol use is 0; 1=never heavy (all past points in time g/d alcohol <60 (men) as the reference; 2=heavy alcohol use in the past (≥60 (men) at least at one age in the past).

<sup>c</sup>Categorization of calcium intake was performed based on the population distribution in the calcium variable (continuous) and according to the daily intake recommendations found in the following document:

<https://ods.od.nih.gov/factsheets/Calcium-DatosEnEspanol/> (very low: ≤743.68 mg/day; low: >743.68mg/day—<1,000 mg/day and normal: ≥1,000 mg/day).

*BMI* body mass index

**Supplementary Table 2.** Population characteristics according nitrosyl-heme intake in women within European Prospective Investigation into Cancer and Nutrition

| Women                                                 |                         | Nitrosyl-heme intake (µg/d) |        |          |          |
|-------------------------------------------------------|-------------------------|-----------------------------|--------|----------|----------|
|                                                       |                         | N (%)                       | p25    | Median   | p75      |
| <b>Total</b>                                          |                         | 258,343 (70.3)              | 208.56 | 559.25   | 1,205.15 |
| <b>Age (y)</b>                                        |                         |                             |        |          |          |
|                                                       | <33                     | 12,955 (5.0)                | 3.00   | 42.8     | 312.49   |
|                                                       | ≥33-<44                 | 42,734 (16.5)               | 146.03 | 512.83   | 1,244.08 |
|                                                       | ≥44 - <54               | 100,878 (39.0)              | 270.30 | 661.37   | 1,359.94 |
|                                                       | ≥54- <64                | 81,423 (31.5)               | 246.96 | 585.39   | 1,190.79 |
|                                                       | ≥64                     | 20,353 (7.9)                | 169.88 | 423.54   | 890.16   |
| <b>BMI (kg/m2)</b>                                    |                         |                             |        |          |          |
|                                                       | <25                     | 153,505 (59.4)              | 178.73 | 527.80   | 1,177.77 |
|                                                       | ≥25-30                  | 73,873 (28.6)               | 239.20 | 583.13   | 1,209.21 |
|                                                       | ≥30                     | 30,965 (12.0)               | 260.57 | 638.58   | 1,343.0  |
| <b>Country</b>                                        |                         |                             |        |          |          |
|                                                       | France                  | 67,403 (26.1)               | 406.71 | 883.86   | 1,689.43 |
|                                                       | Italy                   | 30,513 (11.8)               | 168.61 | 363.85   | 677.77   |
|                                                       | Spain                   | 24,850 (9.6)                | 189.18 | 485.18   | 952.74   |
|                                                       | UK                      | 52,566 (20.3)               | 21.40  | 141.91   | 388.88   |
|                                                       | The Netherlands         | 26,912 (10.4)               | 282.84 | 677.98   | 1,268.69 |
|                                                       | Germany                 | 27,379 (10.6)               | 798.63 | 1,555.27 | 2,526.11 |
|                                                       | Denmark                 | 28,720 (11.1)               | 363.05 | 687.67   | 1,161.48 |
| <b>Waist circumference (cm)<sup>a</sup></b>           |                         |                             |        |          |          |
|                                                       | Normal                  | 164,711 (63.8)              | 146.94 | 448.67   | 1,026.12 |
|                                                       | High                    | 46,040 (17.8)               | 272.57 | 641.80   | 1,309.33 |
|                                                       | Missing/Unknown         | 47,592 (18.4)               | 409.89 | 896.97   | 1,716.80 |
| <b>Cambridge Physical Activity Index (Met-h/week)</b> |                         |                             |        |          |          |
|                                                       | Inactive                | 58,179 (22.5)               | 181.86 | 471.98   | 1,057.04 |
|                                                       | Moderately Inactive     | 92,544 (35.8)               | 217.48 | 571.87   | 1,231.51 |
|                                                       | Moderately Active       | 62,166 (24.1)               | 230.96 | 620.00   | 1,316.27 |
|                                                       | Active                  | 41,713 (16.1)               | 196.39 | 559.39   | 1,177.02 |
|                                                       | Missing/Unknown         | 3,741 (1.4)                 | 238.92 | 647.80   | 1,282.47 |
| <b>Educational level</b>                              |                         |                             |        |          |          |
|                                                       | None                    | 10,691 (4.1)                | 171.43 | 458.57   | 934.01   |
|                                                       | Primary School          | 57,388 (22.2)               | 266.16 | 593.24   | 1,207.89 |
|                                                       | Technical, professional | 52,184 (20.2)               | 231.77 | 602.46   | 1,264.28 |
|                                                       | Secondary School        | 62,279 (24.1)               | 247.26 | 641.00   | 1,332.04 |
|                                                       | Longer Education        | 62,874 (24.3)               | 128.92 | 477.82   | 1,191.12 |
|                                                       | Not specified           | 12,927 (5.0)                | 61.19  | 307.64   | 709.16   |
| <b>Smoking status</b>                                 |                         |                             |        |          |          |
|                                                       | Never                   | 149,478 (57.9)              | 193.94 | 541.75   | 1,190.21 |
|                                                       | Former                  | 58,477 (22.6)               | 188.42 | 528.79   | 1,159.99 |
|                                                       | Current                 | 45,386 (17.6)               | 258.33 | 630.05   | 1,288.73 |
|                                                       | Missing/Unknown         | 5,002 (1.9)                 | 299.04 | 744.78   | 1,496.63 |
| <b>Alcohol lifetime (g/day)<sup>b</sup></b>           |                         |                             |        |          |          |
|                                                       | Non alcohol             | 23,095 (8.9)                | 168.39 | 437.14   | 927.23   |
|                                                       | Never heavy             | 229,218 (88.7)              | 216.09 | 574.08   | 1,231.17 |
|                                                       | Heavy                   | 6,030 (2.3)                 | 112.92 | 523.18   | 1,307.85 |
| <b>Family history of colorectal cancer</b>            |                         |                             |        |          |          |
|                                                       | Yes                     | 88,146 (34.1)               | 282.64 | 662.32   | 1,336.23 |
|                                                       | No                      | 7,689 (3.0)                 | 290.95 | 675.87   | 1,365.71 |
|                                                       | Not specified           | 162,508 (62.9)              | 158.48 | 491.82   | 1,129.50 |
| <b>Calcium (mg/day)<sup>c</sup></b>                   |                         |                             |        |          |          |
|                                                       | Very Low                | 63,506 (24.6)               | 183.96 | 512.40   | 1,147.10 |
|                                                       | Low                     | 76,608 (29.7)               | 219.79 | 562.88   | 1,197.35 |
|                                                       | Normal                  | 118,229 (45.8)              | 215.47 | 581.92   | 1,242.03 |
| <b>Fibre (g/day)</b>                                  |                         |                             |        |          |          |
|                                                       | <30                     | 219,044 (84.8)              | 224.97 | 575.52   | 1,214.54 |

|           |               |       |        |          |
|-----------|---------------|-------|--------|----------|
| $\geq 30$ | 39,299 (15.2) | 79.60 | 436.67 | 1,149.70 |
|-----------|---------------|-------|--------|----------|

<sup>a</sup>Waist circumference (cm) (normal: <88cm ; high:  $\geq 88$ cm; missing/unknown).

<sup>b</sup>Alcohol lifetime (g/day) (0=no alcohol in the past, i.e. at all ages in the past the alcohol use is 0; 1=never heavy (all past points in time g/d alcohol <30 (women)) as the reference; 2=heavy alcohol use in the past ( $\geq 30$  (women) at least at one age in the past).

<sup>c</sup>Categorization of calcium intake was performed based on the population distribution in the calcium variable (continuous) and according to the daily intake recommendations found in the following document:

<https://ods.od.nih.gov/factsheets/Calcium-DatosEnEspanol/> (very low:  $\leq 743.68$  mg/day; low:  $> 743.68$  mg/day–<1,000 mg/day and normal:  $\geq 1,000$  mg/day).

*BMI* body mass index

**Supplementary Table 3 .** Risk of colorectal cancer and tumour subtypes from nitrosyl-heme intake: hazard ratios and 95% CI, EPIC study sensitivity analyses

| Sex-specific tertiles of nitrosyl-heme intake                |         |                |                  |                   |         |                                                |                  |
|--------------------------------------------------------------|---------|----------------|------------------|-------------------|---------|------------------------------------------------|------------------|
|                                                              | N cases | HR (95% CI) T1 | HR (95% CI) T2   | HR (95% CI) T3    | p-trend | Continuous (per 400 µg increment) <sup>a</sup> | AIC <sup>b</sup> |
| <b>Colorectal Cancer</b>                                     |         |                |                  |                   |         |                                                |                  |
| <b>Excluding the first 5 years of follow-up</b>              |         |                |                  |                   |         |                                                |                  |
| Model 1                                                      | 3,928   | Referent       | 1.04 (0.96-1.13) | 1.01 (0.92-1.11)  | 0.86    | 1.01 (1.00-1.02)                               | 48,795.8         |
| Model 2                                                      |         | Referent       | 1.03 (0.95-1.11) | 0.99 (0.90-1.09)  | 0.83    | 1.00 (0.99-1.01)                               | 48,662.2         |
| <b>Additional excluding participants from UK<sup>c</sup></b> |         |                |                  |                   |         |                                                |                  |
| Model 1                                                      | 3,131   | Referent       | 1.03 (0.95-1.13) | 0.98 (0.89-1.09)  | 0.79    | 1.00 (0.99-1.01)                               | 38,937.0         |
| Model 2                                                      |         | Referent       | 1.02 (0.93-1.11) | 0.97 (0.88- 1.08) | 0.66    | 1.00 (0.98-1.01)                               | 38,833.1         |
| <b>Distal Colon Cancer</b>                                   |         |                |                  |                   |         |                                                |                  |
| <b>Excluding the first 5 years of follow-up</b>              |         |                |                  |                   |         |                                                |                  |
| Model 1                                                      | 1,051   | Referent       | 0.99 (0.85-1.16) | 1.01 (0.84-1.21)  | 0.92    | 1.01 (0.98-1.03)                               | 12,991.1         |
| Model 2                                                      |         | Referent       | 0.99 (0.54-1.15) | 1.00 (0.84-1.21)  | 0.93    | 1.00 (0.97-1.02)                               | 12,936.4         |
| <b>Additional excluding participants from UK<sup>c</sup></b> |         |                |                  |                   |         |                                                |                  |
| Model 1                                                      | 876     | Referent       | 1.00 (0.85-1.18) | 0.97 (0.80-1.17)  | 0.79    | 1.00 (0.98-1.02)                               | 10,799.2         |
| Model 2                                                      |         | Referent       | 1.00 (0.85-1.18) | 0.98 (0.81-1.19)  | 0.86    | 0.99 (0.97-1.02)                               | 10,759.6         |
| <b>Proximal Colon Cancer</b>                                 |         |                |                  |                   |         |                                                |                  |
| <b>Excluding the first 5 years of follow-up</b>              |         |                |                  |                   |         |                                                |                  |
| Model 1                                                      | 1,134   | Referent       | 1.05 (0.91-1.22) | 1.01 (0.85-1.20)  | 0.89    | 0.99 (0.97-1.02)                               | 13,954.0         |
| Model 2                                                      |         | Referent       | 1.04 (0.90-1.20) | 0.98 (0.82-1.17)  | 0.84    | 0.98 (0.96-1.01)                               | 13,908.2         |
| <b>Additional excluding</b>                                  |         |                |                  |                   |         |                                                |                  |

|                                                                  |       |          |                  |                  |      |                  |          |
|------------------------------------------------------------------|-------|----------|------------------|------------------|------|------------------|----------|
| participant<br>s from UK <sup>2</sup>                            |       |          |                  |                  |      |                  |          |
| Model 1                                                          | 865   | Referent | 1.08 (0.92-1.27) | 1.04 (0.85-1.26) | 0.67 | 0.99 (0.96-1.01) | 10,679.8 |
| Model 2                                                          |       | Referent | 1.06 (0.90-1.26) | 1.01 (0.83-1.22) | 0.79 | 0.98 (0.95-1.01) | 10,644.5 |
| Colon<br>Cancer                                                  |       |          |                  |                  |      |                  |          |
| Excluding<br>the first 5<br>years of<br>follow-up                |       |          |                  |                  |      |                  |          |
| Model 1                                                          | 2,351 | Referent | 1.03 (0.93-1.14) | 1.04 (0.92-1.17) | 0.53 | 1.00 (0.99-1.02) | 29,051.3 |
| Model 2                                                          |       | Referent | 1.02 (0.92-1.13) | 1.02 (0.90-1.15) | 0.79 | 0.99 (0.98-1.01) | 28,936.6 |
| Additional<br>excluding<br>participant<br>s from UK <sup>c</sup> |       |          |                  |                  |      |                  |          |
| Model 1                                                          | 1,871 | Referent | 1.07 (0.96-1.20) | 1.04 (0.91-1.18) | 0.51 | 1.00 (0.98-1.02) | 23,133.9 |
| Model 2                                                          |       | Referent | 1.06 (0.94-1.18) | 1.02 (0.90-1.17) | 0.68 | 0.99 (0.97-1.01) | 23,043.4 |
| Rectal<br>Cancer                                                 |       |          |                  |                  |      |                  |          |
| Excluding<br>the first 5<br>years of<br>follow-up                |       |          |                  |                  |      |                  |          |
| Model 1                                                          | 1,222 | Referent | 1.07 (0.93-1.24) | 0.93 (0.79-1.11) | 0.42 | 1.01 (0.99-1.03) | 15,360.6 |
| Model 2                                                          |       | Referent | 1.05 (0.90-1.21) | 0.91 (0.77-1.09) | 0.31 | 1.00 (0.98-1.02) | 15,350.4 |
| Additional<br>excluding<br>participant<br>s from UK <sup>c</sup> |       |          |                  |                  |      |                  |          |
| Model 1                                                          | 980   | Referent | 1.00 (0.85-1.17) | 0.94 (0.79-1.12) | 0.51 | 1.01 (0.99-1.03) | 12,320.9 |
| Model 2                                                          |       | Referent | 0.98 (0.84-1.15) | 0.94 (0.78-1.13) | 0.25 | 1.00 (0.98-1.02) | 12,319.3 |

<sup>a</sup>Models were run per 400µg of increment of nitrosyl-heme intake. Models were adjusted for sex, height, weight, education, physical activity, smoking, calcium intake, fibre intake, alcohol lifetime consumption and for energy intakes and stratified by age at recruitment and centre.

<sup>b</sup>AIC Akaike information criterion

<sup>c</sup>Mostly vegetarians

**Supplementary Table 4.** Association between processed meat intake and colorectal cancer (CRC) risk by duration of follow-up

| Follow-up period | Model   | HR (95% CI) T1 | HR (95% CI) T2   | HR (95% CI) T3   | p-trend | Continuous HR (95% CI) | No. of events |
|------------------|---------|----------------|------------------|------------------|---------|------------------------|---------------|
| 2 years          | Model 2 | Referent       | 1.18 (0.84–2.31) | 0.87 (0.51–1.93) | 726     | 1.07 (0.93–1.24)       | 401           |
| 5 years          | Model 2 | Referent       | 0.87 (0.70–1.09) | 0.98 (0.76–1.27) | 822     | 0.99 (0.95–1.02)       | 1,187         |
| 8 years          | Model 2 | Referent       | 0.99 (0.86–1.15) | 0.99 (0.83–1.18) | 920     | 1.00 (0.98–1.03)       | 2,106         |
| 11 years         | Model 2 | Referent       | 0.92 (0.83–1.03) | 1.02 (0.90–1.16) | 819     | 1.00 (0.98–1.02)       | 3,188         |
| 14 years         | Model 2 | Referent       | 0.98 (0.89–1.07) | 0.99 (0.90–1.11) | 899     | 0.99 (0.97–1.00)       | 4,296         |
| 20 years         | Model 2 | Referent       | 0.95 (0.88–1.04) | 0.99 (0.90–1.09) | 851     | 0.99 (0.98–1.00)       | 5,115         |

Model 1: stratified by age and centre, and adjusted for sex and energy intake.

Model 2: Model 1 and further adjusted by: height (in cm), weight (in kg), education level (none, primary school, technical/professional school, secondary school, longer education, and unknown), smoking status (never, former, and current), waist circumference (low: <88 cm in women & <102 cm in men; high: ≥88cm in women & ≥102cm in men), physical activity (inactive, moderately inactive, moderately active, active, unknown/missing), lifetime alcohol consumption (as continuous variable), fibre (as continuous variable), calcium (very low: ≤743.68 mg/day; low: >743.68mg/day–<1,000 mg/day and normal: ≥1,000 mg/day).